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A systematic review and meta-analysis of the use of anticoagulation in the management of neonatal cerebral sinovenous thrombosis

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Abstract

Aims: to determine whether anticoagulation therapy in the treatment of neonatal cerebral sinovenous thrombosis (CSVT) improves outcomes, in the presence or absence of pre-existing intracerebral haemorrhage (ICH).

Methods: We searched CENTRAL; MEDLINE; Embase; CINAHL and the Web of Science, and clinical trial databases. We considered data from both retrospective and prospective cohort studies, case series, and randomised controlled studies evaluating outcomes of CSVT treated with anticoagulation or no anticoagulation.

Studies were included if they involved infants either less than 28 days of age, or less than 44 weeks post-menstrual age at time of diagnosis of CSVT in which anticoagulation was considered.

Results: Seven non-randomised studies were included in meta-analysis. Anticoagulation therapy had no significant effect on mortality prior to discharge either in the presence or absence of pre-existing ICH, nor on the incidence of extension of pre-existing ICH. Anticoagulation therapy was associated with a reduced risk of propagation of thrombus (RR 0.14 95%CI 0.03-0.72).

Interpretation: There are no randomised trials assessing the safety and efficacy of anticoagulation therapy in the treatment of neonatal CSVT. The results of this meta-analysis would justify a position of equipoise and support the need for well designed randomised controlled trials of anti-coagulation therapy in this population.

Short form title: Anticoagulation in neonatal cerebral sinovenous thrombosis

What this paper adds:

- There are no randomised controlled studies evaluating the use anticoagulation therapy in neonatal CSVT
- Anticoagulation therapy may reduce thrombus propagation
- No evidence of increased morbidity or mortality with anticoagulation therapy was demonstrated
- A position of equipoise is justified, supporting the need for placebo controlled randomised trials

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Introduction

Cerebral sino venous thrombosis (CSVT) has a peak incidence in the neonatal period, with an incidence estimated between 2 and 12 per 100,000 live newborns.(1, 2) It is associated with significant morbidity, including visual deficits,(2) seizures,(2) sensorimotor impairments (3) and mortality.(2) The clinical presentations of neonatal CSVT are varied. Although seizures are the most frequently reported presenting feature, lethargy or reduced consciousness, apnoea, hyper or hypotonia, focal motor deficits and respiratory distress have all been reported.(2-5) CSVT may also be detected in asymptomatic infants imaged for unrelated reasons. (2, 4) Pathogenesis is multifactorial and includes various maternal and neonatal factors, as well as prothrombotic coagulant factors.

CSVT also occurs in adults and children, where the mainstay of treatment is anticoagulation with unfractionated or low-molecular-weight heparin to increase the rate of resolution, and prevent the propagation of thrombus. This may reduce the extent of thrombus related venous infarct, and haemorrhagic transformation. This treatment is supported by a reasonable evidence base in the adult population (6) and there is some evidence for its use in the pediatric population.(7) Nonetheless, there remains extensive variation in practice in both populations.(8, 9)

There is ongoing uncertainty over the use of anticoagulation in neonatal CSVT. It may be considered to be an entity discreet from pediatric and adult CSVT both due to the unique but transient risk factors present in the neonatal period and the particular fragility of the neonatal brain.(10) Furthermore, this population has a high incidence of pre-existing intracerebral haemorrhage (ICH) at the time of diagnosis. Treatment with anticoagulation therapy could then carry a potential risk of extending existing haemorrhage resulting in poorer outcomes.

The use of anticoagulation therapy in the management of neonatal CSVT has been included in several guidelines (7, 11) yet its use in infants with pre-existing ICH remains contentious. Few studies have attempted to assess the safety and efficacy of anticoagulation therapy in neonatal CSVT, and crucially, the evidence for ACT has not been considered in infants with pre-existing ICH where treatment decisions may be the most challenging.

In this systematic review we assess the evidence for anticoagulation therapy in the treatment of neonatal CSVT both in the presence and absence of pre-existing ICH. Our objective was to test the hypothesis that anticoagulation therapy in the treatment of CSVT improves mortality rate and long-term neurological outcome in neonates. We further hypothesised that treatment is also beneficial in infants with pre-existing ICH, despite a theoretical increased risk of extension of haemorrhage.

Objectives

To determine whether anticoagulation therapy in the treatment of cerebral sinovenous thrombosis in neonates (less than 28 days age, or less than 44 weeks post-menstrual age at presentation and with or without pre-existing ICH) is associated with lower mortality prior to discharge, reduced risk of extension of pre-existing haemorrhage, reduced rates of thrombus propagation and improved neurodevelopmental outcomes at two years of age.

Methods

No protocol was published in advance of this systematic review and meta-analysis.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library); MEDLINE via Ovid SP (January 1966 to 1st October 2017); EMBASE vias Ovid SP

(January 1980 to 1st October 2017); CINAHL via EBSCO Host (1982 to 1st October 2017) and Web of Science (1985 to 1st October 2017). We used the Cochrane highly sensitive search strategy for identifying randomised controlled trials as suggested in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). MeSH headings were used when available as shown in Table 1. An additional free text search was conducted for each search engine using: "Newborn" AND (" Cerebral venous" OR "cerebral sinovenous") AND ("thrombus" OR "thrombosis")

In addition we searched the following registries: http://www.controlled-trials.com; http://clinicaltrials.gov; http://www.anzctr.org.au

We also checked the reference lists of all identified studies for further relevant studies. Conference abstracts were not included in the systematic review, but were used to identify published papers.

Data collection and analysis

Selection of studies, data extraction and management

After identifying studies using the electronic databases, the bibliographies were reviewed to identify additional relevant studies, and a full text second stage screening was performed by 2 reviewers (TR, RS). Initial records were screened for relevance, and the abstracts of those records of potential relevance were reviewed. Studies that potentially fulfilled inclusion criteria based on the abstract were reviewed as full text. A decision was made as to eligibility for inclusion, and any disagreement between reviewers was resolved by discussion.

A standardised data extraction form was used by both reviewers.(12)

Another reviewer (TA) assessed the quality of studies independently and any differences were reconciled by mutual agreement.

The details of all excluded studies are listed with reason for exclusion in Table 2.

Inclusion criteria

We considered data from both retrospective and prospective cohort studies, case series, randomised controlled studies evaluating outcomes of CSVT treated with anticoagulation or no anticoagulation.

Studies were included if they involved infants either less than 28 days of age, or less than 44 weeks post-menstrual age at time of diagnosis of CSVT in which anticoagulation was considered in the presence or absence of intracranial haemorrhage.

Primary outcomes considered were death or neurological sequelae at 2 years follow-up and death prior to discharge from hospital.

Secondary outcomes considered were extension of thrombus, and extension of intracranial haemorrhage.

Characteristics of included studies are summarised in Table 3.

Assessment of risk of bias in included studies

Risk of bias was independently assessed by two reviewers (TR,RS) using the Cochrane Collaboration's domain based tool for assessing risk of bias. Selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias were scored. An overall risk of bias for each study was 'high risk of bias', 'low risk of bias' or 'unclear risk of bias'. This was made according to guidance in the Cochrane Handbook for Systematic Reviews of Interventions(13). Any disagreements were resolved by consensus, or where necessary, discussion with TA.

Measures of treatment effect

Categorical data were extracted for each intervention group and the risk ratio (RR) and risk difference (RD) calculated. If the risk difference was statistically significant the number needed to treat or harm was calculated.

Assessment of heterogeneity

Heterogeneity was quantified with the I^2 statistic calculated as described in the Cochrane Handbook for Systematic Reviews of Interventions.(13) The thresholds for interpreting I^2 are:

· 0% to 40%: may represent insignificant heterogeneity

· 30-60%: may represent moderate heterogeneity

· 50-90%: may represent substantial heterogeneity

· >75%: may represent considerable heterogeneity

Were I^2 to exceed 75% we would have conducted a sensitivity analysis to explain the source of heterogeneity.

Assessment of reporting biases

Where meta-analysis was undertaken a funnel plot was used to assess publication bias.

Data synthesis

Meta-analysis was performed using RevMan using a fixed-effect model where there were two or more studies with comparable populations and treatment interventions.

We present our results with 95% CIs. We assessed RRs and RDs. The outcomes of comparable trials were analysed with 95% CIs to estimate treatment effect. If appropriate, we compared results using forest plots with the RR as the point estimate for dichotomous outcomes.

Results:

Figure 1.

Seven studies presented outcomes from neonatal CSVT with sufficient detail to be included in meta-analysis and are shown in Table 3. Authors assessment of bias is presented in Figure 2. Fitzgerald et al. performed a single center retrospective review of 42 patients with neonatal CSVT, of whom 25 had pre-existing ICH. Three without ICH received anticoagulation.(4) Gentilomo et al. conducted a single center retrospective review identifying five neonates with CSVT of whom two received anticoagulation therapy.(14) Kenet et al. identified eight cases of neonatal CSVT in a multicenter case control study, four of which received anticoagulation therapy.(15) Kersbergen et al. identified ten cases of neonatal CSVT in a single center of whom seven received anticoagulation therapy.(16) Moharir et al. published two retrospective analyses of cases of neonatal CSVT that were prospectively enrolled into a study.

In the first study containing 83 cases of neonatal CSVT, 59 neonates had ICH at presentation of whom 21 received anticoagulation therapy. Of the remaining 24 without ICH at presentation, 17 received anticoagulation therapy.(17)

In the latter study, 71 of 104 neonates had ICH at presentation, of whom 29 received anticoagulation therapy. Of the remaining 33 without ICH at presentation, 24 received anticoagulation therapy.(3) The data from patients in the earlier study were included in the later study. Incomplete reporting of outcome variables required inclusion of the earlier study where data were not presented in the larger study. (3) Pergami et al. conducted a retrospective review of neonatal CSVT identifying 22 cases of whom five received anticoagulation therapy without complication.(18)

In none of the studies was treatment allocated by randomization. Decision to treat was based in all cases on local protocols, and individual clinicians assessment of the likelihood of benefit. This would be a significant source of bias in the results of all the included studies.

Sufficient data were reported to meta-analyse the effect of anticoagulation therapy on mortality prior to discharge in neonates with pre-existing ICH and without. (Figures 3 to 6)

In neonates without pre-existing ICH there was no effect of anticoagulant therapy on mortality prior to hospital discharge (RR 0.91; 95% CI: 0.23-3.57). There was a non-significant trend towards lower mortality prior to hospital discharge in neonates with pre-existing ICH who received anticoagulation therapy compared to those who did not (RR 0.14; 95% CI 0.02-1.21).

Two studies presented sufficient data to meta-analyse the effect of anticoagulation therapy on the incidence of extension of ICH in neonates with pre-existing ICH.(16, 18) This showed a non-significant trend towards lower rates of extension of haemorrhage in those that received anticoagulant therapy (RR 0.35; 95% CI: 0.05-2.34). (Figures 7 & 8)

A meta-analysis of two studies demonstrated a lower risk of propagation of thrombus in neonates that received anti-coagulation therapy compared to those that did not (irrespective of ICH status) (RR 0.09; 95% CI: 0.02-0.47). (Figure 9 & 10)

While several studies reported neurodevelopmental outcomes (2-4, 14, 16, 17, 19) in all cases the time point and variable tools for assessment precluded comparison. In one study predictors of poor neurological outcome at last follow-up were examined. Not receiving anticoagulation therapy was a predictor of poorer neurodevelopmental outcome on univariate but not multivariate analysis.(17)

No meta-analysis of outcome data was possible.

Discussion

In this meta-analysis in hospital mortality did not differ significantly between those who received anticoagulation therapy and those that did not. However, there was a trend towards lower mortality in those infants with pre-existing ICH receiving anticoagulation therapy.

Our meta-analysis suggests a significantly reduced risk of thrombus propagation in neonates with CSVT who receive anticoagulation therapy. There was no greater risk of new or extension of haemorrhage in those infants with pre-existing ICH who received anticoagulation therapy compared to those who did not.

While there is reasonable evidence for the use of anticoagulation in CSVT in adults (20) and some evidence for safety and efficacy in children, (7) there is limited data to guide usage of anticoagulation therapy in neonates with CSVT. Nonetheless there are expert consensus guidelines which provide varied degrees of support for the use of anticoagulation in neonates.(11, 21, 22) Although we identified several studies which reported the use of anticoagulation therapy for CSVT in the neonatal population, they were limited to retrospective reviews of cases.(2, 4, 5, 14-16, 23, 24) Of interest, none of these studies reported a significantly higher rate of intracranial haemorrhage in neonates that received anticoagulation therapy. In contrast, in the largest prospective study identified, Moharir et al. reported a slightly higher but non-significant rate of major ICH in 6% of anticoagulated neonates compared to 3% of untreated neonates (p=0.536).(17) Our meta-analysis of the few studies which reported outcomes according to both the presence of pre-existing ICH and anticoagulation therapy suggested that the risk of extension in infants with pre-existing ICH is not increased by anticoagulation therapy.

In this meta-analysis the risk of death prior to discharge was not higher in infants who received anticoagulation therapy compared to controls either in the presence or absence of

pre-existing ICH. In the presence of ICH there was a trend towards lower mortality in those that received anticoagulation therapy. However, as the use of anticoagulation would have been based on clinician assessment (and perceived stability) of individual infants, there is high risk of selection bias and these results must be interpreted with caution.

This meta-analysis demonstrated a significant benefit of anticoagulation therapy in reducing the risk of thrombus propagation. Propagation of thrombus has been associated with an increased rate of subsequent venous infarction.(3)

Of note, many of the included neonates were initiated on anticoagulation therapy only following demonstrated propagation of thrombus after diagnosis and an initial clinical decision not to treat, with associated close monitoring with imaging. Those that were not commenced on anticoagulation therapy were monitored for propagation with MRV, whereas those treated were more likely to be imaged using CT to assess for anticoagulation therapy related haemorrhage.(3) The reduced sensitivity of CT in detecting thrombus would make a degree of detection bias highly likely, with those reimaged with MRV more likely to have extension detected.

There is a reasonable explanation for the benefit of anticoagulation, as haemorrhage in the context of neonatal CSVT is most likely to arise from venous infarction due to raised venous pressure. While the risk of bias is high in these studies, there appears to be some support for a benefit of anticoagulation therapy in reducing thrombus propagation. This may plausibly decrease venous pressures and therefore reduce both further parenchymal damage through venous infarction and the risk of haemorrhagic transformation.

The studies included in this review comprised a heterogeneous population.

Numerous risk factors for CSVT and ICH vary between the term and preterm population. The studies included in this systematic review included both term and prematurely born infants,

however none of the studies presented data in such a way that these two groups could be analysed separately. This is an important consideration for future studies, as the risks and benefits of anticoagulation therapy may differ between these two populations. Furthermore, studies addressed the varying underlying causes of CSVT differently. Pergami et al. excluded infants with CSVT secondary to CNS infection which were included in other studies. Short and long term outcomes may be heavily influence by the precipitating condition yet it was not possible to explore this with the studies currently available.

Across the studies there is variation in the anticoagulation therapy used; in the timing of anticoagulation therapy (which in some cases was delayed until thrombus propagation was demonstrated); in the agents used; the dosing regime and duration of treatment. While treatment regimes have been proposed (7) these are based on expert opinion. As most of the published studies in the treatment of neonatal CSVT are retrospective, this has not been formally evaluated.

The meta-analysis has been performed on a small number of small, non-randomised studies and therefore caution must be exercised in interpreting the results.(25) Nonetheless, it has allowed a comparison of studies to be undertaken and demonstrated some consistency in findings, which may inform future research design.(26)

Conclusion

Treatment with anticoagulation therapy is variably employed in the management of neonatal CSVT, but there remains insufficient data to assess its safety and efficacy. While the results of this meta-analysis provide some support for the use of anticoagulation therapy in this population, the studies included are at high risk of bias, and caution must be exercised in their interpretation. However, the results of this meta-analysis would justify a

position of equipoise and support the need for well designed randomised controlled trials of anti-coagulation therapy in this population.

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Resource	Search terms
Cochrane central register of controlled trials	(infant, newborn[MeSH Terms]) AND (Sinus thrombosis, intracranial[MeSH Terms])
MEDLINE	(infant, newborn[MeSH Terms]) AND ((Cerebral thrombosis[MeSH Terms]) OR (Cranial sinus thrombosis[MeSH Terms]))
EMBASE	Newborn AND cerebral thrombosis (including related terms)
CINAHL via EBSCO	(MH "Infant, Newborn+") AND ((MH "Intracranial Thrombosis+") OR (MH "Sinus Thrombosis, Intracranial+"))
Web of Science	TOPIC(infant, newborn) AND TOPIC (cerebral venous sinus thrombosis)
www.controlled-trials.com	Text search: "Newborn" AND (" Cerebral venous" OR "cerebral sinovenous") AND ("thrombus" OR "thrombosis")
clinicaltrials.gov	Text search: "Newborn" AND (" Cerebral venous" OR "cerebral sinovenous") AND ("thrombus" OR "thrombosis")
www.anzctr.org.au	Text search: "Newborn" AND (" Cerebral venous" OR "cerebral sinovenous") AND ("thrombus" OR "thrombosis")

Table 1: Search terms employed, by search engine

Study	Reason for exclusion
Berfelo 2010 (2)	Study included 52 neonates, 43 with pre-existing ICH. Now outcomes were presented with sufficient detail for meta-analysis
DeVeber 1998(27)	Study included 8 neonates however no outcome data could be extracted as presented as part of a larger paediatric study
DeVeber 2001(28)	Study included 69 neonates with CSVT, however no outcome data could be extracted for relevant groups (neonates receiving or not receiving ACT)
Grunt 2010(29)	21 neonates with CSVT. Insufficient data presented to include in meta-analysis
Jordan 2010(5)	84 neonates with CSVT, 43 of whom received antithrombotic medication. No data for specified outcome measures could be extracted.
Kenet 2007(19)	75 neonates with CSVT. Unable to extract data for specified outcome measures depending on administration of ACT.
Steinlin 2005(30)	17 CSVT in paediatric population. Unable to extract neonatal data for specified outcome measures
Tuckuviene 2011(23)	7 Neonates included. Unable to extract data for specified outcome measures
Vieira 2010(24)	Possibly 6 neonates included, though varying use of terminology. Not possible to extract data for specified outcome measures.
Wasay 2008(31)	25 neonates included. Not possible to extract data for specified outcome measures

Table 2: Characteristics of excluded studies

	Methods	Participants	Interventions	Outcomes
Fitzgerald 2006	Retrospective single centre study	42 neonates, six were "premature". 25 with pre-existing IVH	3 received ACT with heparin. Non-randomised: treatment at clinicians discretion	Cognitive or motor impairment, epilepsy at last follow-up, in hospital death
Gentilomo 2008	Retrospective single centre study	5 neonates, gestation uncertain. Presented on median day 4 of life (range 1-6).	2 received ACT with LMWH. Non-randomised: treatment at clinicians discretion	In hospital mortality. Neurological sequelae at last clinic
Kenet 2004	Multicentre case control	8 neonates, none born prematurely (gestation or age at presentation not given)	4 received ACT with LMWH. Non-randomised: treatment at clinicians discretion	Death, neurological sequelae
Kersbergen 2009	Retrospective single centre study	10 neonates with CSVT and unilateral thalamic haemorrhage. 32-42 weeks gestation. Presented at median day 5 of life (range 0-19 days)	7 received anticoagulation therapy with LMWH. Non-randomised: treatment at clinicians discretion	Death, recanalization, neurological sequelae
Moharir 2010	Retrospective single centre study	Neonates and children. 83 Neonates included irrespective of gestation	29 received ACT with LMWH, UFH or Warfarin. Non-randomised: treatment at clinicians discretion	ACT-related major haemorrhage, propagation,recanalization, and clinical outcome (favorable or unfavorable (Neurological sequelae or death)).
Moharir 2011	Retrospective multicentre study	104 Neonates diagnosed with CSVT, irrespective of gestation. Gestation of neonates not reported. Presented at median 6 days of age (range 0-27)	53 neonates received ACT with LMWH or UFH. Non-randomised: treatment at clinicians discretion	Death, thrombus propagation, recanalization, neurodevelopmental outcome (variable time points of assessment)
Pergami 2011	Retrospective multicentre study	22 Neonates with confirmed CSVT, 6 preterm (gestational age 31-35 weeks). Age at presentation 1-21 days. Infants with CNS infection excluded.	Rehydration in 18, anticoagulation in 5 with LMWH. Non-randomised: treatment at clinicians discretion	Death before discharge, thrombus propagation, new or extension of haemorrhage

Table 3: Characteristics of included studies

Figure 1: Study flow diagram.

Figure 2: Risk of bias summary: review authors' judgements about risk of bias item for each included study. Red (-) demonstrates high risk of bias. Yellow (?) demonstrates unclear risk of bias

Figure 3: Effect of anticoagulation on mortality before hospital discharge in neonatal CSVT without pre-existing ICH

Figure 4: Funnel plot of studies evaluating the effect of anticoagulation on mortality before hospital discharge in neonatal CSVT without pre-existing ICH

Figure 5: Effect of anticoagulation on mortality before hospital discharge in neonatal CSVT with pre-existing ICH

Figure 6: Funnel plot of studies evaluating the effect of anticoagulation on mortality before hospital discharge in neonatal CSVT with pre-existing ICH

Figure 7: Effect of anticoagulation on incidence of extension of ICH in neonatal CSVT with pre-existing ICH

Figure 8: Funnel plot of studies evaluating the effect of anticoagulation on incidence of extension of ICH in neonatal CSVT with pre-existing ICH

Figure 9: Effect of anticoagulation on risk of propagation of thrombus

Figure 10: Funnel plot of studies evaluating the effect of anticoagulation on risk of propagation of thrombus